LETTERS TO THE EDITOR

Effect of inhaled nitric oxide on left ventricular and pulmonary vascular function

To the Editor:

The conclusions of Argenziano and associates[1] contradicted their evidence. They concluded: "Inhaled nitric oxide reduced pulmonary vascular resistance but did not alter myocardial contractility or diastolic function." However, their Table I showed the following evidence of increased left heart failure after their 6 experimental pigs inhaled nitric oxide (NO): Cardiac output and ejection fraction decreased while left ventricular end-diastolic volume and pressure increased. The authors cited 3 reports that left atrial pressure increased and pulmonary edema appeared when subjects with left ventricular dysfunction inhaled NO therapeutically. This was further evidence that myocardial contractility and diastolic function deteriorated after inhalation of NO.

The authors' second point was that NO lowered the pulmonary vascular resistance (PVR), which they calculated by the standard formula that is derived from Poiseuille's equation.[2] However, "since the experiments from which the equation was derived were performed in straight, rigid tubes with steady, streamlined flow of an ideal, viscous fluid, the relationship cannot be directly applied to the vascular system, in which the vessels are neither straight nor rigid, the blood is not a simple viscous fluid, and the flow is not always streamlined."[2]

The common formula for "vascular resistance" is:

$$PVR = \frac{PAP - LAP}{\text{Cardiac output}}$$

where PAP is mean pulmonary artery pressure and LAP is mean left atrial pressure.

This can be misleading, because raising the left atrial pressure, which Argenziano and colleagues[1] observed in their pigs, decreases the numerator and thereby the calculated PVR. This can happen with no change in pulmonary artery pressure. Raising the left atrial pressure obviously obstructs pulmonary blood flow, but it decreases the calculated PVR. A similarly misleading result occurs when this formula is applied to systemic vascular resistance while phenylephrine (Neo-Synephrine) is administered: The right atrial pressure increases more than the mean arterial pressure increases, thereby decreasing the numerator in the resistance equation. As a result, while vasoconstriction decreases the force of the femoral pulses, the calculated systemic vascular resistance becomes abnormally low, the opposite of the true state.

Although the number of pigs was too small to allow adequate statistical evaluation of some measured parameters, the authors did show well that during controlled heart failure inhaled NO decreased pulmonary artery pressure despite elevated left atrial pressure.

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REFERENCES

1. Argenziano M, Dean DA, Moazami N, Goldstein DJ, Rose EA, Spotnitz HM, et al. Inhaled oxide is not a myocardial depressant in a porcine model of heart failure. J Thorac Cardiovasc Surg 1998;115:700-8.
2. Schlant RC, Sonnenblick EH, Katz AM. Normal physiology of the cardiovascular system. In: Alexander RW, Schlant RC, Fuster V, editors. Hurst's The heart. 9th ed. New York: McGraw-Hill Health Professions Division; 1983. p. 103.

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Reply to the Editor:

We appreciate Dr Krohn's interest in our study and the opportunity to address his comments regarding our assessment of myocardial function and the limitations associated with calculation of pulmonary vascular resistance. We respectfully disagree with Dr Krohn's assertion that our conclusions contradict our evidence. As mentioned in our article, previous reports of pulmonary edema and left atrial pressure elevation after administration of inhaled nitric oxide (iNO) in patients with myocardial dysfunction raised concerns about potential myocardial depressant effects of this agent. Our study was undertaken specifically to assess the effects of this pulmonary vasodilator on myocardial systolic and diastolic function. Because clinical hemodynamic parameters such as cardiac output and left ventricular end-diastolic pressure (LVEDP) are influenced by a number of factors (including preload, afterload, contractility, heart rate, and diastolic compliance) in a complex fashion, these parameters cannot be individually used to accurately assess myocardial contractility or diastolic compliance unless all other factors (ie, preload, afterload, and heart rate) are accounted for. Therefore we assessed systolic function by 2 well-accepted load-independent measures of contractility, the preload-recruitable stroke work relationship (PRSWR) and the end-systolic pressure-volume relationship (ESPVR). We assessed diastolic function by the end-diastolic pressure-volume relation (EDPVR). Our data demonstrated clearly that despite slight increases in LVEDP, contractility and diastolic function as assessed by these measures was not altered by administration of iNO. Dr Krohn cites statistically insignificant decreases in cardiac output and increases in left ventricular volume from Table I of our article as "evidence for deterioration of myocardial contractility and diastolic dysfunction," but he ignores increases in mean arterial pressure and systemic vascular resistance and

decreases in central venous pressure and heart rate, listed in the same table, all of which are consistent with a decrease in cardiac output in the absence of reduced contractility.

With respect to Dr Krohn's comments regarding the limitations associated with the application of the widely used standard pulmonary vascular resistance (PVR) equation, we are in agreement that this method of PVR calculation is imperfect for the reasons he has enumerated. However, Dr Krohn seems to confuse PVR (affected by pulmonary vascular properties) with right ventricular afterload (affected additionally by left atrial pressure, LAP). Pulmonary vasodilation may reduce PVR while raising LAP, thus leaving PAP and right ventricular afterload relatively unchanged.[1] This ought not be viewed as misleading; rather it is simply a natural consequence of the right and left sides of the hearts being connected in series. Furthermore, inasmuch as previous clinical and experimental work have already well established the pulmonary vasodilatory effects of iNO, this was not the focus of our experiment. Rather, since clinically and experimentally observed increases in LAP may be due to a decrease in PVR and/or alterations in ventricular function, we sought to establish whether iNO affects left ventricular systolic or diastolic properties, as described above. We found that the increase in LAP was not due to depression of ventricular function, but was simply a consequence of pulmonary vasodilation.

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REFERENCE

1. Dickstein ML, Burkhoff D. A theoretic analysis of the effect of pulmonary vasodilation on pulmonary venous pressure: implications for inhaled nitric oxide therapy. J Heart Lung Transplant 1996;15:715-21.

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Deep hypothermic circulatory arrest and retrograde cerebral perfusion

To the Editor:

I was disturbed when I read the article by Okita and associates concerning deep hypothermic circulatory arrest (DHCA) and retrograde cerebral perfusion (RCP) in patients undergoing operations on the aortic arch in the January 1998 issue of the Journal (1998;115:129-38). I have several major concerns about the paper. The most important concern relates to the fact that the authors are describing a relatively new technique of cerebral protection, namely RCP, and yet they have failed to include among their investigators or authors any neurologists or psychologists. There is no statement in the methods section of the paper regarding complete neurologic examination of their patients and whether this was performed before and after the operations. My own experience would suggest that a simple retrospective chart review relying on observations by surgical residents is inadequate to detect subtle focal neurologic deficits. For example, how many of these patients had careful assessment of their visual fields? How many patients had their postoperative fine motor skills compared with their preoperative fine motor skills? In fact, even a neurologic examination will not detect many of the cognitive deficits that can only be identified by careful psychometric testing. In the absence of such testing, it is unjustified for the authors to make the statement: "We empirically consider that a DHCA + RCP period of up to 80 minutes under a nasopharyngeal temperature of 18°C is safe." This statement is all the more questionable after viewing Fig 1, which demonstrates that patients who underwent a combined DHCA + RCP time of 70 to 80 minutes had an incidence of death or delirium that was greater that 50%. The authors state: "Postoperative transient delirium has been defined as a transient minor neurologic deficit such as disorientation and character change with no neurologic sequelae." This statement bears resemblance to the previously often heard statement within pediatric cardiac surgery that seizures in the early postoperative period in infants are of no long-term significance. Our prospective randomized trial of DHCA[1] has demonstrated that perioperative seizures do indeed have an association with subsequent impairment, as assessed by our developmental psychologists using comprehensive testing at age 1 year and 4 years with ongoing studies of this same cohort at age 8 years.

Until clinical studies have been undertaken with careful preoperative and postoperative neurologic examination by neurologists, as well as psychometric testing, I believe that surgeons should be cautious in using RCP as a means of extending DHCA. If it is possible to extrapolate from the pediatric experience with DHCA, periods of DHCA greater that 30 to 45 minutes in length at a tympanic membrane temperature of 15°C should be used with great caution.

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REFERENCE

1. Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KCK, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 1995;332:549-55.

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To the Editor:

We thank Dr Jonas for his informative response regarding our article and appreciate his contributions to this field in pediatric cardiac surgery.

We did have neurologists or radiologists involved in this study. They did preoperative or postoperative neurologic examinations of our patients or reviewed the radiologic images. We must apologize for not including their names among the authors of our paper and for not stating their con-